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Branch atheromatous disease and treatment

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Abstract:

Branch atheromatous disease (BAD) is a subtype of ischemic stroke caused by perforating arteries occlusion due to proximal atherosclerosis of the arteries. Early neurological deterioration and recurrent stereotyped transient ischemic attacks are typical clinical manifestations of BAD. The optimal treatment for BAD has not been determined. This article explores a possible mechanism of BAD and effective treatment measures to prevent early progression and attack of transient ischemic events. This article explains the current status of intravenous thrombolysis, tirofiban, and argatroban for BAD and subsequent prognosis.

Keywords:

Argatroban, branch atheromatous disease, early neurological deterioration, intravenous thrombolytic therapy, tirofiban

Introduction

Branch atheromatous disease (BAD)[1] is a common subtype of acute ischemic stroke (AIS), accounting for 10%–15% of the cases. It was first named by Caplan in 1989 and described with early neurological deterioration (END), or recurrent stereotyped transient ischemic attacks (TIAs). END occurs in 17%–75% of BAD-related strokes[2,3] within 48–72 h of the initial onset.[4,5] The most common arteries causing END include the lenticulostriate artery (LSA) and paramedian pontine artery. END has a high risk of worsening stroke symptoms, which makes patients very anxious. In fact, END cannot be effectively hampered by intravenous thrombolytic, antiplatelet, and other traditional stroke treatments,[6] and often leads to adverse functional outcomes (i.e. modified Rankin score [mRS] >1) in patients with BAD-related stroke.[7] New and more effective treatment modalities are needed for END.

The mechanism of BAD and END is largely unknown. The current studies and limited pathological results indicate that the pathogenesis of BAD is related to atherosclerosis of large vessels. Pentraxin 3 (PTX3) is a prototypical member of the pentraxin family and its levels are found to be increased in cardiovascular and cerebrovascular diseases with atherosclerotic lesions.[8] Ninomiya *et al*. explain that elevated serum PTX3 levels can predict the diagnosis of BAD at a very early stage of cerebrovascular diseases.[9] High-resolution and whole-brain vessel-wall MRI images can find culprit plaques adjacent to the deep penetrating arteries in BAD[10] and even minimal plaques distal to LSA in lacunar infarction (LI), caused by lipohyalinosis[11] from intrinsic cerebral small vessel disease.

Treatments

Treatments for BAD-related AIS include intravenous thrombolytic therapy (IVT), antiplatelet, anticoagulation, statins, and volumetric therapy. Based on the mechanism of thrombosis, IVT is theoretically the most effective treatment for END. A study of 135 patients with AIS shows that 51 patients who received alteplase were more likely to

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be functionally independent (mRS = 0–2) at 3 months with a markedly lower rate of death or dependence, compared to the control group.[12]

However, it has been questioned whether recombinant tissue plasminogen activator (rt-PA) can effectively prevent the progression of BAD as the clinical improvement from rt-PA may be temporary. It has been reported that about 57.1% of AIS cases develop a relapse of symptoms even after the administration of IVT.[2,7,13] END usually occurs 48–72 h after the onset of stroke, which exceeds the time window for IVT. Although it has been advocated that IVT beyond 4.5 h is clinically effective for awake patients with an unknown onset time of stroke under the guidance of imaging, it is still not suitable to administer IVT for END after this time frame.

Tirofiban, a low-molecular-weight nonpeptide platelet GP IIb/IIIa receptor antagonist, has been used for selected patients with AIS. Tirofiban administration for END within the first 24 h of IVT is not found to increase the risk of intracranial hemorrhage but is associated with neurological improvement at 3 months.[14,15] Safety of Tirofiban in acute Ischemic Stroke trial explains that an initial infusion of 0.4 μg/kg body weight/minute over 30 min followed by a continuous infusion of 0.1 μg/kg body weight/minute for 48 h is reasonable for progressive stroke from small artery occlusion.[16] Symptoms and clinical deficits associated with progressive ischemic stroke are found to be attenuated by tirofiban administration in dual antiplatelet therapy (DAPT). There is no significant risk of systemic hemorrhage or cerebral infarction hemorrhage associated with tirofiban or DAPT.[17] Unfortunately, existing studies show conflicting findings about tirofiban for BAD-related END. A study with a small sample advocates the use of intravenous tirofiban to stop early symptomatic fluctuations and shorten the duration of functional deficits in patients with capsular warning syndrome or symptoms of BAD, characterized by recurrent episodes of TIA ≥3 times in 24 h.[18] A randomized clinical trial involving 948 patients in China with stroke and proximal intracranial large vessel occlusion notes that intravenous tirofiban, compared with placebo, before endovascular therapy resulted in no significant difference in disability severity at 90 days.[19]

The combination of antiplatelet agents and anticoagulants is not routinely given for ischemic cerebrovascular disease due to the increased risk of bleeding. Furthermore, DAPT or anticoagulant therapy alone does not effectively prevent the occurrence and progression of BAD. However, DAPT with argatroban can be safely administered for AIS or TIA.[20] A Japanese study has shown that the combination of argatroban, aspirin, and clopidogrel prevents END.[21] The speculated mechanism is lumen stenosis from BAD with arteriosclerosis, forming a red thrombus after platelet adhesion to the vessel lumen. Argatroban, a direct thrombin inhibitor, exerts its anticoagulant effect by binding to dissolving and coagulating thrombin.[22] DAPT with argatroban may prevent platelet activation and the formation of white or red thrombus; a retrospective study suggests this treatment option to prevent END from BAD.[23]

Patients with BAD can present with severe motor impairment, like the clinical findings from a large cerebral artery occlusion (LCAO). In contrast to LCAO, the language function and consciousness level are generally preserved with BAD.[24] Therefore, distinguishing BAD from LCAO is important to maximize the benefit of endovascular treatment. Although some studies suggest new treatment options to minimize the occurrence of BAD-related END and improve the prognosis, they are based on small samples.[2,7,13,18] Large-sample randomized studies are needed to establish reliable treatment plans at this point.

Regardless of the fluctuating symptoms of END, the functional prognosis of BAD is usually found to be between that of major artery occlusion and LI.[25] The long-term outcome of END is like that of LI and most patients tend to have good prognosis (i.e., mRS,2) after 3 months.[13] Patients with BAD require long-term inpatient rehabilitation.[26,27] Male gender, young age, and supratentorial lesions are associated with better functional improvement.[28]

Finally, concurrent psychological counseling with pharmacological treatment can help patients understand the nature of this infarction type, which ultimately reduces mental tension and encourages participation in rehabilitation exercises for maximal recovery.

Conclusion

BAD is one of the imperative causes of AIS and is characterized by early symptomatic progression. Therapies for BAD are limited. IVT appears to be the best option for patients in the treatment time window without contraindications. Although evidence for tirofiban or argatroban alone or with IVT is limited, no significant harm has been confirmed with these agents. Tirofiban or argatroban with DAPT can be considered for BAD.

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Conflicts of interest

Dr. Yuchuan Ding is an Associate Editor, Dr. Xiaokun Geng is an Editorial Board member of *Brain Circulation*.

The article was subject to the journal's standard procedures, with peer review handled independently of them and their research groups.

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